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The Rayleigh-Plesset equation for a liquid-crystalline shelled microbubble

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ABSTRACT: Premanufactured shelled microbubbles are currently used in the medical profession as ultrasound imaging agents. Recent research is focussing on using these shelled microbubbles for localised drug delivery. Presently, there exists no mathematical model for a liquid-crystalline shelled microbubble. For the very first time, using Leslie-Erikson theory, a theoretical model is developed for a gas loaded shelled microbubble that is composed of a nematic liquid-crystalline material. Current mathematical models assume that the shells are viscoelastic in nature and are typically modelled as a Maxwell fluid. However, this approach is totally inappropriate for a liquid-crystalline material which is non-Newtonian in nature. We show that liquid-crystalline shelled microbubbles possess different physical properties from commercial shelled microbubbles. We have found that nematic liquid-crystalline shelled microbubbles have a relaxation time that is 10 times longer than certain commercial shelled microbubbles. The authors propose that these significantly different physical properties may enhance localised drug delivery via sonoporation. This is due to their longer relaxation time which enhances acoustic microstreaming and significantly increases the magnitude of the wall shear stress.

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I. INTRODUCTION

Recent research is focussing on using shelled microbubbles as a mechanism for localised drug delivery [1–6]. There are several types of commercial shelled microbubbles, also known as ultrasound contrast agents (UCAs). The shelled microbubbles have a typical radius of several microns thus allowing them to move through the capillaries and a shell thickness of several nanometres [7]. Shelled microbubbles resonate with frequencies of the order of several megahertz and display higher harmonic signals [8]. There has been a significant growth in recent years into using UCAs for localised drug delivery [9]. We intend to develop simulation tools to better understand the challenges involved.

Current shelled microbubble models use a Rayleigh-Plesset equation which is derived by applying pressure balances to the inner and outside of the shelled microbubble's surface and the surrounding liquid [10–12]. Our Rayleigh-Plesset equation assumes that the microbubble oscillations are radially directed and that the surrounding Newtonian liquid is incompressible. We assume that the gas in the shelled microbubble behaves adiabatically [12]. We have accounted for the viscous damping associated with the microbubble shell but have not considered thermal and acoustic dissipation.

Thin monolipid microbubbles have shells that are viscoelastic in nature, and behave more

like a fluid than a solid shell [12]. This fluid like behaviour has inspired us to consider one specific type of mesophase material, nematic liquid crystals. We propose an entirely new type of shelled microbubble which is composed of a thin nematic liquid-crystalline shell. This type of shelled microbubble has a different material composition from all existing commercial shelled microbubbles. This paper uses the Leslie-Erikson continuum theory ([13], p133-159) for liquid crystals to model the dynamic behaviour of a gas loaded, shelled microbubble. This is the first study that has used nematic liquid crystal theory to model UCAs. Note that all the previous published literature pertaining to the modelling of shelled microbubbles focusses solely on the use of Newtonian viscoelastic models. The use of models such as Kelvin-Voigt and the Maxwell fluid model is wholly inappropriate for the modelling of a liquid-crystalline shell. Nematic liquid crystals are non-Newtonian fluids and typically exhibit anisotropic behaviour. We show that nematic liquid-crystalline shells display significantly different physical characteristics from commercial shells: these physical characteristics, namely the longer relaxation time and the significantly lower damping term are highly advantageous to the mechanism of sonoporation [14].

The paper is structured in the following way: Section 2 deals with the generic Rayleigh-Plesset equation then Section 3 focusses on the evaluation of the stress of the liquid crystal's shell with Section 4 considering the elastic energy density of the shell. Section 5 determines the linearised Rayleigh-Plesset model and Section 6 compares a liquid-crystalline shelled microbubble to a commercial UCA.

II. THE RAYLEIGH-PLESSET MODEL

Consider a shelled microbubble with inner and outer radii given by R_1 and R_2 respectively, where the radii are functions of time only and the density of the shell is denoted by ρ_s . This article uses a dot notation above a physical quantity to represent differentiation of that quantity with respect to time. In terms of tensor notation, let x_i represent the positional coordinate and $r = |\mathbf{x}|$ where $r^2 = x_i x_i$. We shall denote the radial unit vector as \mathbf{e}_r and the speed and acceleration of the inner radius of the microbubble as \dot{R}_1 and \ddot{R}_1 respectively. Let ρ_L denote the density of the surrounding incompressible liquid where σ represents the Cauchy stress. Momentum balance results in the following equation to describe the dynamics of the UCA [10,15,16]

$$\left(R_1 \ddot{R}_1 \left(1 - \left(\frac{\rho_s - \rho_L}{\rho_s} \right) \frac{R_1}{R_2} \right) + \dot{R}_1^2 \left(\frac{3}{2} - \left(\frac{\rho_s - \rho_L}{\rho_s} \right) \left(\frac{4R_1 R_2^3 - R_1^4}{2R_2^4} \right) \right) \right) \mathbf{e}_r = \frac{1}{\rho_s} \int_{R_1}^{\infty} (\nabla \cdot \sigma) dr, \quad (1)$$

where a pressure balance has to be applied in order to determine the right hand side of equation (1). The pressure of the gas phase inside the shell and the surrounding ambient fluid pressure have to be considered as do the surface tensions and the shell and fluid viscosities. The divergence of the stress σ can be expressed as

$$\nabla \cdot \sigma = -\nabla P + \nabla \cdot \tau,$$

where P denotes a pressure term and τ represents both the stress in the shell and the stress due to the surrounding Newtonian fluid. Rewriting the right hand side of equation (1) and integrating over the various media leads to

$$\begin{aligned} \int_{R_1}^{\infty} (\nabla \cdot \sigma) dr &= \int_{R_1}^{\infty} (-\nabla P + \nabla \cdot \tau) dr \\ &= (P_S(R_1, t) - P_S(R_2, t) + P_L(R_2, t) - P_{\infty}(t)) \mathbf{e}_r + \int_{R_1}^{R_2} (\nabla \cdot \tau_S) dr + \int_{R_2}^{\infty} (\nabla \cdot \tau_L) dr, \end{aligned} \quad (2)$$

where P_S , P_L and P_∞ are the pressures in the shell, the surrounding Newtonian fluid, and at infinity, respectively. The stresses in the shell and the stress associated with the viscosity of the surrounding fluid are denoted by τ_S and τ_L respectively. Let R_{01} and R_{02} denote the equilibrium (unperturbed) inner and outer radius of the shelled microbubble. The boundary conditions at the inner and outer radii of the shell's surface respectively are found by applying the momentum balance law [10] which leads to

$$P_S(R_1, t) = P_g \left(\frac{R_{01}}{R_1} \right)^{3\kappa} + \tau_{S,rr}(R_1, t) - \frac{2\gamma_1}{R_1}, \quad (3)$$

$$P_S(R_2, t) = P_L(R_2, t) + \tau_{S,rr}(R_2, t) + \frac{2\gamma_2}{R_2} - \tau_L(R_2, t), \quad (4)$$

where κ denotes the polytropic index which is a dimensionless parameter [10, 17] and $\tau_{S,rr}$ denotes the stress in the radial direction. The terms γ_1 and γ_2 denote the interfacial surface tension (gas-shell interface) and the surface tension between the outer shell and the surrounding liquid respectively. The gas pressure P_g in equation (3) is obtained by balancing the pressures at the equilibrium radii R_{01} and R_{02} to give

$$P_g = P_0 + \frac{2\gamma_1}{R_{01}} + \frac{2\gamma_2}{R_{02}} + S, \quad (5)$$

where P_0 represents the surrounding ambient liquid pressure and S is the stress associated with the elastic energy density of the liquid crystal and is given by equation (23) in Section 4. Note that P_∞ in equation (2) describes the atmospheric pressure plus any external applied pressures (such as those created by an ultrasound probe) and is represented by $P_\infty = P_0 + P_A \sin \omega t$ where P_A and ω represent the externally applied pressure and angular frequency respectively. Substituting equations (3) and (4) into equation (2) gives

$$\begin{aligned} \int_{R_1}^{\infty} (\nabla \cdot \sigma) dr = & \left(P_g \left(\frac{R_{01}}{R_1} \right)^{3\kappa} + \tau_{S,rr}(R_1, t) - \tau_{S,rr}(R_2, t) - \frac{2\gamma_1}{R_1} - \frac{2\gamma_2}{R_2} - P_0 \right) e_r \\ & + (-P_A \sin \omega t + \tau_L(R_2, t)) e_r \\ & + \int_{R_1}^{R_2} (\nabla \cdot \tau_S) dr + \int_{R_2}^{\infty} (\nabla \cdot \tau_L) dr. \end{aligned} \quad (6)$$

The stress due to the viscosity μ_L of the surrounding Newtonian fluid is denoted by $\tau_L(R_2, t)$ where ([10], [18] p50)

$$\tau_L(R_2, t) = -4\mu_L \frac{\dot{R}_2}{R_2}, \quad (7)$$

whereas the term $\int_{R_2}^{\infty} (\nabla \cdot \tau_L) dr$ in equation (6) ([19], p354-p355) results in

$$\int_{R_2}^{\infty} (\nabla \cdot \tau_L) dr = \mu_L \int_{R_2}^{\infty} \left(\frac{1}{r^2} \frac{\partial}{\partial r} \left(r^2 \frac{\partial v}{\partial r} \right) - \frac{2v}{r^2} \right) e_r dr = 0. \quad (8)$$

III. CALCULATING THE STRESS OF A LIQUID CRYSTAL SHELL

This section focusses on deriving an expression for the viscous stress of an incompressible liquid-crystal shell of known inner and outer radii. It is assumed that the shell's composition is a liquid crystal that can be described dynamically using the nematic theory developed by Leslie and Ericksen ([13], p133-159) where five independent Leslie viscosities [20] are required to determine the stress in the shell. The sixth Leslie viscosity can be written as a linear combination of some of the other five independent Leslie viscosities. Some proteins [21] exhibit the characteristic behaviour of a liquid crystal where the molecules are arranged in layers ([13], p6). This paper will use nematic theory to

model the mesophase behaviour of proteins [22]. Continuum modelling of liquid-crystal theory assumes that the molecules are rod like in nature and are described by a unit vector \mathbf{n} which is called the director. The molecules are arranged in layers with the director aligning perpendicular to the layers and parallel to the layer normal ([13],p6). We shall assume spherical symmetry of the liquid-crystalline shell with the director pointing radially outward everywhere and the layers consisting of concentric spheres. The director describes the local direction of the average molecular alignment and is a unit vector (so $\mathbf{n} = \mathbf{e}_i x_i / r$) ([13],p6), where x_i represents the positional coordinate and $r = |\mathbf{x}|$. The viscous stress τ_{ij} for a nematic liquid-crystal is given by

$$\tau_{ij} = \alpha_1 n_k A_{kp} n_p n_i n_j + \alpha_2 N_i n_j + \alpha_3 n_i N_j + \alpha_4 A_{ij} + \alpha_5 n_j A_{ik} n_k + \alpha_6 n_i A_{jk} n_k, \quad (9)$$

where $\alpha_1, \alpha_2, \alpha_3, \alpha_4, \alpha_5$ and α_6 are the Leslie viscosities, A_{ij} is the rate of strain tensor and N_i is the co-rotational time flux of the director \mathbf{n} . The corotational time flux is a measure of the rotation of the director, \mathbf{n} , relative to the fluid. These terms are explicitly defined as $n_i = x_i / r$, $A_{ik} = (v_{i,k} + v_{k,i}) / 2$, $N_i = \dot{n}_i - W_{ij} n_j$ where the superposed dot signifies the material time derivative $\dot{n}_i = \partial n_i / \partial t + v_j \partial n_i / \partial x_j$ and $W_{ij} = (v_{i,j} - v_{j,i}) / 2$ is the vorticity tensor. For the spherically symmetric case we have a velocity profile given by $\mathbf{v} = v \mathbf{e}_r$ which is rewritten as

$$v_i = \frac{v x_i}{r}. \quad (10)$$

Hence

$$v_{i,k} = \frac{v \delta_{ik}}{r} + x_i \frac{\partial}{\partial r} \left(\frac{v}{r} \right) \frac{\partial r}{\partial x_k}.$$

Since $r^2 = x_k x_k$ then

$$\frac{\partial r}{\partial x_k} = \frac{x_k}{r}. \quad (11)$$

and so

$$v_{i,k} = \frac{v \delta_{ik}}{r} + \frac{x_i x_k}{r} \frac{\partial}{\partial r} \left(\frac{v}{r} \right), \quad (12)$$

and since $\delta_{kp} = \delta_{pk}$ then

$$A_{kp} = \frac{v \delta_{kp}}{r} + \frac{x_k x_p}{r} \frac{\partial}{\partial r} \left(\frac{v}{r} \right), \quad (13)$$

with $N_i = 0$ and $W_{ij} = 0$. Substituting into equation (9) gives

$$\begin{aligned} \tau_{ij} = & \frac{\alpha_1 x_i x_j v}{r^3} + \frac{\alpha_1 x_i x_j}{r} \frac{\partial}{\partial r} \left(\frac{v}{r} \right) + \frac{\alpha_4 v \delta_{ij}}{r} + \frac{\alpha_4 x_i x_j}{r} \frac{\partial}{\partial r} \left(\frac{v}{r} \right) \\ & + \frac{\alpha_5 v x_j x_i}{r^3} + \frac{\alpha_5 x_j x_i}{r} \frac{\partial}{\partial r} \left(\frac{v}{r} \right) + \frac{\alpha_6 x_i x_j v}{r^3} + \frac{\alpha_6 x_i x_j}{r} \frac{\partial}{\partial r} \left(\frac{v}{r} \right). \end{aligned} \quad (14)$$

The shelled microbubble is assumed to be an incompressible shell composed of a thin liquid crystal shell with a radially directed flow ([13],p139). Since the shell is incompressible then its volume, V , and density will be time independent. For a shelled microbubble with an inner and outer radii given by R_1 and R_2 respectively, the following relationship holds

$$\frac{dV}{dt} = \frac{d}{dt} \left(\frac{4}{3} \pi (R_2^3 - R_1^3) \right) = 0,$$

from which we can deduce that

$$R_1^2 \dot{R}_1 = R_2^2 \dot{R}_2. \quad (15)$$

Church [10] and Doinikov et al. [15] state that

$$\frac{v}{r} = \frac{R_1^2 \dot{R}_1}{r^3}, \quad (16)$$

and so

$$\frac{\partial}{\partial r} \left(\frac{v}{r} \right) = \frac{-3R_1^2 \dot{R}_1}{r^4}. \quad (17)$$

Using equations (16) and (17), the Leslie viscosities represented by equation (14) can be rewritten as

$$\begin{aligned} \tau_{ij} = & \frac{-2\alpha_1 x_i x_j R_1^2 \dot{R}_1}{r^5} + \frac{\alpha_4 R_1^2 \dot{R}_1 \delta_{ij}}{r^3} - \frac{3\alpha_4 x_i x_j R_1^2 \dot{R}_1}{r^5} \\ & - \frac{2\alpha_5 R_1^2 \dot{R}_1 x_i x_j}{r^5} - \frac{2\alpha_6 R_1^2 \dot{R}_1 x_i x_j}{r^5}. \end{aligned} \quad (18)$$

To determine the Cauchy momentum represented by equation (1) we have to evaluate the divergence of equation (18). Writing this in component form results in

$$\frac{\partial \tau_{ij}}{\partial x_i} = \frac{2\alpha_1 R_1^2 \dot{R}_1 x_j}{r^5} + \frac{2\alpha_5 R_1^2 \dot{R}_1 x_j}{r^5} + \frac{2\alpha_6 R_1^2 \dot{R}_1 x_j}{r^5}, \quad (19)$$

where the α_4 contribution is zero which is consistent with Brennan ([18], p49-50). The stress associated with the Leslie viscosities is calculated by integrating equation (19) between the inner and outer radius of the shell. Our mathematical model focusses on purely radial oscillatory behaviour. Since the shelled microbubble moves solely in the radial direction then in spherical polar coordinates $\mathbf{r} = r\mathbf{e}_r$, with $r^2 = x_j x_j$. The j th cartesian component of \mathbf{e}_r is given by x_j/r . Evaluating the integral between R_1 and R_2 results in

$$\int_{R_1}^{R_2} (\nabla \cdot \boldsymbol{\tau}) dr = \frac{2}{3} (\alpha_1 + \alpha_5 + \alpha_6) \left(\frac{\dot{R}_1}{R_1} - \frac{R_1^2 \dot{R}_1}{R_2^3} \right) \mathbf{e}_r. \quad (20)$$

IV. THE ELASTIC ENERGY DENSITY FOR A SHELLED MICROBUBBLE

The liquid-crystal shell has both a viscous stress associated with the Leslie viscosities and a stress due to the elastic energy of the liquid crystal. This latter stress will add a further term to equation (9) as calculated below. The following strain energy density function was proposed for a bilipid membrane by De Vita and Stewart [21]

$$W = \frac{1}{2}K_{1a}(\nabla \cdot a)^2 + \frac{1}{2}K_{1n}(\nabla \cdot n)^2 + \frac{1}{2}B_0|\nabla\Psi|^{-2}(1-|\nabla\Psi|)^2 + \frac{1}{2}B_1(1-(n \cdot a)^2) + B_2(\nabla \cdot n)(1-|\nabla\Psi|^{-1}), \quad (21)$$

where K_{1a} , K_{1n} , B_0 , B_1 and B_2 are material constants, a is the unit normal to the layer, Ψ defines the layer structure of a liquid crystal and $|\Psi|^{-1}$ represents the current local interlayer distance. The first term on the right hand side of equation (21) refers to the bending energy while the second term represents the splay energy contribution. The B_0 term represents the compression-expansion energy, B_1 is the energy associated with the coupling between n and a , and B_2 is the term associated with the coupling between the splay and compression- expansion of the layer. It is assumed that the shelled microbubble is a bilipid membrane with a typical thickness of 4nm ([13], p4). Generally $|\Psi|^{-1} = 1$ although for an undistorted liquid-crystal such as planar layers it is useful to define $|\nabla\Psi|^{-1}$ such that $|\nabla\Psi|^{-1} \neq 1$. There is no contribution to the strain energy density function from the B_0 , B_1 and B_2 terms given in equation (21). There are no published values for K_{1a} but K_{1n} is known for several types of liquid-crystalline material ([13], p330). We shall make the assumption that $K_{1a} \approx K_{1n}$ such that $K_{1a} = K_{1n} = K_1$. This assumption is based on the experimentally determined values of K_{1n} for various types of liquid crystals, all of which are very similar in magnitude. Assuming that $n = a$ then we can conclude that the contribution from the elastic energy density reduces to

$$W = K_1(\nabla \cdot n)^2. \quad (22)$$

The stress associated with the elastic constant arising from the splay and the bending energies given by $K_1(n_{i,i})^2$ is determined via $(-\partial W/\partial n_{p,j}) n_{p,i}$ and is represented by $\tau_{elastic}$ ([13],p151) where W is given by equation (22). So

$$\begin{aligned} (\tau_{elastic})_{ij} &= -\frac{\partial W}{\partial n_{p,j}} n_{p,i}, \\ &= -2K_1(n_{p,p}) n_{j,i}, \\ &= -2K_1 \frac{\partial}{\partial x_p} \left(\frac{x_p}{r} \right) \frac{\partial}{\partial x_i} \left(\frac{x_j}{r} \right). \end{aligned}$$

The integral of the divergence of the stress associated with the elastic energy density contributions due to n and a is

$$\int_{R_1}^{R_2} (\nabla \cdot \tau_{elastic}) dr = -4K_1 \left(\frac{1}{R_2^2} - \frac{1}{R_1^2} \right) e_r. \quad (23)$$

Combining equations (20) and (23) gives the total stress in the shell as

$$\int_{R_1}^{R_2} (\nabla \cdot \tau_S) dr = \frac{2}{3} (\alpha_1 + \alpha_5 + \alpha_6) \left(\frac{\dot{R}_1}{R_1} - \frac{\dot{R}_2}{R_2} \right) e_r + 4K_1 \left(\frac{1}{R_1^2} - \frac{1}{R_2^2} \right) e_r, \quad (24)$$

where τ_S represents the total stress in the shell. Substituting equations (7), (8), (18) and (24) into equation (6) gives

$$\begin{aligned} \int_{R_1}^{\infty} (\nabla \cdot \sigma) dr = & \left(P_g \left(\frac{R_{01}}{R_1} \right)^{3\kappa} - \frac{4}{3} (\alpha_1 + \alpha_5 + \alpha_6) \left(\frac{\dot{R}_1}{R_1} - \frac{\dot{R}_2}{R_2} \right) - 4K_1 \left(\frac{1}{R_1^2} - \frac{1}{R_2^2} \right) \right) \\ & + \left(-4\mu_L \frac{\dot{R}_2}{R_2} - P_0 - P_A \sin \omega t - \frac{2\gamma_1}{R_1} - \frac{2\gamma_2}{R_2} \right) e_r, \quad (25) \end{aligned}$$

where R_{01} is the unperturbed inner radius. To simplify the notation let $\alpha = \frac{4}{3} (\alpha_1 + \alpha_5 + \alpha_6)$. Using equation (23), the stress S in its unperturbed state is equal to $4K_1 (1/R_{01}^2 - 1/R_{02}^2)$. Substituting equation (25) into the right-hand side of equation (1) leads to

$$\begin{aligned} & R_1 \ddot{R}_1 \left(1 - \left(\frac{\rho_S - \rho_L}{\rho_S} \right) \frac{R_1}{R_2} \right) + \dot{R}_1^2 \left(\frac{3}{2} - \left(\frac{\rho_S - \rho_L}{\rho_S} \right) \left(\frac{4R_1 R_2^3 - R_1^4}{2R_2^4} \right) \right) \\ = & \frac{1}{\rho_S} \left(\left(P_0 + \frac{2\gamma_1}{R_{01}} + \frac{2\gamma_2}{R_{02}} + 4K_1 \left(\frac{1}{R_{01}^2} - \frac{1}{R_{02}^2} \right) \right) \left(\frac{R_{01}}{R_1} \right)^{3\kappa} - \frac{2\gamma_1}{R_1} - \frac{2\gamma_2}{R_2} - P_0 - P_A \sin(\omega t) \right) \\ & - \frac{1}{\rho_S} \left(\alpha \left(\frac{\dot{R}_1}{R_1} - \frac{\dot{R}_2}{R_2} \right) + 4K_1 \left(\frac{1}{R_1^2} - \frac{1}{R_2^2} \right) + \frac{4\mu_L \dot{R}_2}{R_2} \right). \quad (26) \end{aligned}$$

V. LINEARISATION

The technique of linearisation is used to determine the natural frequency and relaxation time for the shelled microbubble whose dynamic behaviour is described by equation (26). The time dependent perturbations for the inner and outer radii can be written as

$$R_1 = R_{01} (1 + \xi(t)), \quad (27)$$

and

$$R_2 = R_{02} (1 + \eta(t)), \quad (28)$$

respectively. The shell is incompressible which results in $R_2^3 - R_1^3 = R_{02}^3 - R_{01}^3$. Linearising $R_2^3 - R_1^3 = R_{02}^3 - R_{01}^3$ using equations (27) and (28) and assuming that $|\xi|, |\eta| \ll 1$, results in

$$R_2^3 - R_1^3 \approx R_{02}^3 (1 + 3\eta) - R_{01}^3 (1 + 3\xi),$$

which can be simplified to give

$$\eta = \left(\frac{R_{01}}{R_{02}} \right)^3 \xi. \quad (29)$$

To linearise equation (26) we have to assume that the externally applied forcing pressure P_A is of the same order of magnitude (in some appropriate sense) as $|\xi|$ and $|\eta|$. Then linearising equation (26) leads to

$$\begin{aligned} & R_{01}^2 \ddot{\xi} \left(1 - \left(\frac{\rho_S - \rho_L}{\rho_S} \right) \frac{R_{01}}{R_{02}} \right) \\ &= \frac{1}{\rho_S} \left(-3\kappa \xi \left(P_0 + \frac{2\gamma_1}{R_{01}} + \frac{2\gamma_2}{R_{02}} + 4K_1 \left(\frac{1}{R_{01}^2} - \frac{1}{R_{02}^2} \right) \right) + \frac{2\gamma_1 \xi}{R_{01}} + \frac{2\gamma_2 \eta}{R_{02}} - P_A \sin(\omega t) \right) \\ &\quad - \frac{1}{\rho_S} \left(\alpha \dot{\xi} \left(1 - \left(\frac{R_{01}}{R_{02}} \right)^3 \right) + \frac{8K_1 \eta}{R_{02}^2} - \frac{8K_1 \xi}{R_{01}^2} + 4\mu_L \dot{\eta} \right). \quad (30) \end{aligned}$$

Dividing equation (30) throughout by R_{01}^2 and substituting equation (29) into it gives

$$\begin{aligned} & \ddot{\xi} \left(1 - \left(\frac{\rho_S - \rho_L}{\rho_S} \right) \frac{R_{01}}{R_{02}} \right) \\ &= \frac{1}{\rho_S R_{01}^2} \left(-3\kappa \xi \left(P_0 + \frac{2\gamma_1}{R_{01}} + \frac{2\gamma_2}{R_{02}} + 4K_1 \left(\frac{1}{R_{01}^2} - \frac{1}{R_{02}^2} \right) \right) + \frac{2\gamma_1 \xi}{R_{01}} + \frac{2\gamma_2}{R_{02}} \left(\frac{R_{01}}{R_{02}} \right)^3 \xi \right) \\ &\quad - \frac{1}{\rho_S R_{01}^2} \left(\alpha \dot{\xi} \left(1 - \left(\frac{R_{01}}{R_{02}} \right)^3 \right) + \frac{8K_1}{R_{02}^2} \left(\frac{R_{01}}{R_{02}} \right)^3 \xi - \frac{8K_1 \xi}{R_{01}^2} + 4\mu_L \left(\frac{R_{01}}{R_{02}} \right)^3 \dot{\xi} + P_A \sin(\omega t) \right). \quad (31) \end{aligned}$$

Note that the linearised equation (31) has the form

$$\ddot{\xi} + 2\gamma_d \dot{\xi} + \omega_o^2 \xi = \frac{P(t)}{\rho_S R_{01}^2 (1 - ((\rho_S - \rho_L)/\rho_S) R_{01}/R_{02})}, \quad (32)$$

where γ_d represents a damping term and ω_o is the angular natural frequency of the shelled microbubble. The term, $P(t)$, represents the sinusoidal, external ultrasound signal which forces the shelled microbubble. The damping term is given as

$$\gamma_d = \frac{\alpha \left(1 - (R_{01}/R_{02})^3 \right) + 4\mu_L (R_{01}/R_{02})^3}{2\rho_S R_{01}^2 (1 - ((\rho_S - \rho_L)/\rho_S) R_{01}/R_{02})}, \quad (33)$$

which is related to the relaxation time by $t_{\text{relax}} = 1/\gamma_d$. The natural frequency, $f_o = \omega_o/(2\pi)$, is given by

$$f_o = \frac{1}{2\pi} \sqrt{\frac{N}{D}}, \quad (34)$$

where

$$N = 3\kappa R_{01} R_{02}^5 (P_0 + 2\gamma_1/R_{01} + 2\gamma_2/R_{02}) - 2\gamma_1 R_{02}^5 - 2\gamma_2 R_{01}^4 R_{02} \\ + (12\kappa - 8)K_1 R_{02}^5/R_{01} + 8K_1 R_{01}^4 - 12\kappa K_1 R_{02}^3 R_{01}, \quad (35)$$

and

$$D = (\rho_S R_{01}^3 R_{02}^5 - (\rho_S - \rho_L) R_{01}^4 R_{02}^4). \quad (36)$$

VI. COMPARISON OF A NEMATIC LIQUID-CRYSTALLINE SHELLED MICROBUBBLE WITH A COMMERCIAL UCA

We shall compare a nematic liquid-crystalline (MBBA) shelled microbubble of thickness $R_{02}-R_{01}$ and outer equilibrium radius of $R_{02} = 1\mu\text{m}$ to an equally sized commercial shelled microbubble discussed by Doinikov and Bouakaz [23]. Let us assume that the densities of the liquid-crystalline shell and the surrounding fluid are $\rho_S = 1060 \text{ kgm}^{-3}$ and $\rho_L = 1000 \text{ kgm}^{-3}$ respectively ([13], p330). The Leslie viscosity term, the polytropic index of the gas, the viscosity of the surrounding fluid and the interfacial surface tension and the exterior radius' surface tension are $\alpha = 0.035 \text{ Pa s}$, $\kappa = 1.095$, $\mu_L = 10^{-3} \text{ Pa s}$, $\gamma_1 = 0.036 \text{ Nm}^{-1}$ and $\gamma_2 = 0.072 \text{ Nm}^{-1}$ respectively ([13], p330). The damping term for a liquid-crystalline shelled microbubble was $\gamma_d = 2.2 \times 10^6 \text{ s}^{-1}$ compared to $\gamma_d = 3.2 \times 10^7 \text{ s}^{-1}$ for the commercial shelled microbubble. This results in a relaxation time of $t_{\text{relax}} = 4.5 \times 10^{-7} \text{ s}$ for a liquid-crystalline shelled microbubble compared to $t_{\text{relax}} = 3.2 \times 10^{-8} \text{ s}$ for a commercial shelled microbubble. Comparing the natural frequencies f_0 for both types of shells where $P_0 = 10^5 \text{ Pa}$ gives $f_0 = 4.6 \text{ MHz}$ for a liquid-crystalline shell compared to $f_0 = 10.8 \text{ MHz}$ for a commercial shelled microbubble. Note that $f_0 = 10.8 \text{ MHz}$ is the mathematically determined natural frequency for a single shelled microbubble. Our study does not consider a uniform suspension of microbubbles or a polydisperse suspension.

Doinikov and Bouakaz have shown that the wall shear stress due to acoustic microstreaming via a shelled microbubble is inversely proportional to the square of the damping term [23]. Cowley and McGinty have speculated that the significantly different value for the damping term for a liquid-crystalline shell and a commercial UCA shell strongly influence the mechanism of sonoporation [14]. Cowley and McGinty have proposed that a liquid-crystalline shelled microbubble enhances the capillary wall shear stress by two orders of magnitude compared to a commercial shelled microbubble. This is a consequence of the smaller damping term for the liquid-crystalline shell. Note that the Cowley and McGinty model is for a rigid plane capillary wall as is the Doinikov and Bouakaz model.

VII. CONCLUSION

A modified Rayleigh-Plesset equation has been derived using Leslie-Erikson theory for a shelled microbubble with an incompressible shell composed of a nematic liquid-crystalline material, surrounded by a Newtonian fluid. The model considered the adiabatic gas inside the shelled microbubble, the thin shell's crystalline material and the surrounding Newtonian fluid. We then linearized the model using time-dependent perturbation theory and determined expressions for the relaxation time and the natural frequency of the shelled microbubble.

Up until now there has been no published experimental data for liquid-crystalline shelled microbubbles. Using the values given by Doinikov and Bouakaz for commercial shelled microbubbles, we have found that the damping term γ_d for commercial microbubbles is approximately 10 times larger than the damping term for a nematic liquid-crystalline shelled microbubble. This implies that current commercial shelled microbubbles have a relaxation time that is approximately 10 times shorter. We have also found that the natural frequency of a liquid-crystalline shelled microbubble is approximately 1/2 that of a commercial shelled microbubble. We speculate that the difference in relaxation times has profound implications for the wall shear stress.

Future research will focus on the technique of sonoporation which involves using the shelled microbubbles in conjunction with an external ultrasound signal to temporarily enhance the porosity of the capillary walls. This temporary enhancement of the walls is a consequence of wall

shear stress and is due to several mechanisms [23]. One such mechanism is acoustic microstreaming which we intend to model using our liquid-crystalline shelled microbubble model. It has been proposed by Doinikov and Bouakaz that both the damping term and the natural frequency of the shell have a significant influence on the magnitude of the wall shear stress. We will compare and contrast the wall shear stress generated by a suspension of liquid-crystalline shelled microbubbles acting on a viscoelastic capillary wall to that generated by a suspension of commercial contrast agents. We accept that experimental data is required in order to validate the findings of our mathematical model. It is the authors' hope that this journal article instigates future experimental work.

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REFERENCES

- [1]. D. Gourevich, A. Volovick, O. Dogadkin, L. Wang, H. Mulvana, Y. Medan, A. Melzer, and S. Cochran. In vitro investigation of the individual contributions of ultrasound-induced stable and inertial cavitation in targeted drug delivery. *Ultrasound in Medicine & Biology*, 41:1853–1864, 2015.
- [2]. J.M. Escoffre, C. Mannaris, B. Geers, A. Novell, I. Lentacker, M. Averkion, and A. Bouakaz. Doxorubicin liposome-loaded microbubbles for contrast imaging and ultrasound triggered drug delivery. *IEEE Transactions on Ultrasonics, Ferroelectrics and Frequency Control*, 60:78–87, 2013.
- [3]. C.H. Fan, C.Y. Ting, H.L. Liu, C.Y. Huang, H.Y. Hsieh, T.C. Yen, K.C. Wei, and C.K. Yeh. Antiangiogenic-targeting drug-loaded microbubbles combined with focused ultrasound for glioma treatment. *Biomaterials*, 34:2142–2155, 2013.
- [4]. F. Yan, L. Li, Z. Deng, Q. Jin, J. Chen, W. Yang, C.K. Yeh, J. Wu, R. Shandas, X. Liu, and H. Zheng. Paclitaxel-liposome-microbubble complexes as ultrasound-triggered therapeutic drug delivery carriers. *Journal of Controlled Release*, 166:246–255, 2013.
- [5]. Delalande, C. Leduc, P. Midoux, M. Postema, and C. Pichon. Efficient gene delivery by sonoporation is associated with microbubble entry into cells and the clathrin-dependent endocytosis pathway. *Ultrasound in Medicine & Biology*, 41:1913–1926, 2015.
- [6]. McEwan, J. Owen, E. Stride, C. Fowley, H. Nesbitt, D. Cochrane, C.C. Coussios, M. Borden, N. Nomikou, A.P. McHale, and J.F. Callan. Oxygen carrying microbubbles for enhanced sonodynamic therapy of hypoxic tumours. *Journal of Controlled Release*, 203:51–56, 2015.
- [7]. J. McLaughlan, N. Ingram, P.R. Smith, S. Harput, P.L. Coletta, S. Evans, and S. Freear. Increasing the sonoporation efficiency of targeted polydisperse microbubble populations using chirp excitation. *IEEE Transactions on Ultrasonics, Ferroelectrics and Frequency Control*, 60:2511–2520, 2013.
- [8]. M.J.K. Blomley, J.C. Cooke, E.C. Unger, M.J. Monaghan, and D.O. Cosgrove. Microbubble contrast agents: a new era in ultrasound. *British Medical Journal*, 322:1222–1225, 2001.
- [9]. Lentacker, S.C. De Smedt, and N.N. Sanders. Drug loaded microbubble design for ultrasound triggered delivery. *Soft Matter*, 5:2161–2170, 2009.
- [10]. C.C. Church. The effects of an elastic solid surface layer on the radial pulsations of gas bubbles. *Journal Acoustical Society of America*, 97:1510–1521, 1995.
- [11]. P. Marmottant, S. Van der Meer, M. Emmer, M. Versluis, N. de Jong, R. Hilgenfeldt, and D. Lohse. A model for large amplitude oscillations of coated bubbles accounting for buckling and rupture. *Journal Acoustical Society of America*, 118:3499–3505, 2005.
- [12]. Doinikov and A. Bouakaz. Review of shell models for contrast agent microbubbles. *IEEE Transactions on Ultrasonics, Ferroelectrics and Frequency Control*, 58:981–993, 2011.
- [13]. I.W. Stewart. *The Static and Dynamic Continuum Theory of Liquid Crystals*. Taylor and Francis, London, 2004.
- [14]. J. Cowley and S. McGinty. A mathematical model of sonoporation using a liquid-crystalline shelled microbubble. *Ultrasonics*, <https://doi.org/10.1016/j.ultras.2019.01.004>.
- [15]. A.A. Doinikov and P.A. Dayton. Maxwell rheological model for lipid-shelled ultrasound microbubble contrast agents. *Journal Acoustical Society of America*, 121:3331–3340, 2007.
- [16]. A.A. Doinikov, J.F. Haac, and P.A. Dayton. Modeling of nonlinear viscous stress in encapsulating shells of lipid-coated contrast agent microbubbles. *Ultrasonics*, 49:269–275, 2009.
- [17]. S. Paul, A. Katiyar, K. Sarkar, D. Chatterjee, W.T. Shi, and F. Forsberg. Material

- characterization of the encapsulation of an ultrasound contrast microbubble and its subharmonic response: Strain-softening interfacial elasticity model. *Journal Acoustical Society of America*, 127:3846–3857, 2010.
- [18]. C. Brennen. *Cavitation and Bubble Dynamics*. Oxford University Press, New York, 1995. D.J. Acheson. *Elementary Fluid Dynamics*. Oxford University Press, New York, 1990.
- [19]. F.M. Leslie. Continuum theory for nematic liquid crystals. *Continuum Mechanics and Thermodynamics*, 4:167–175, 1992.
- [20]. R. De Vita and I.W. Stewart. Energetics of lipid bilayers with applications to deformations induced by inclusions. *Soft Matter*, 9:2056–2068, 2013.
- [21]. I.W. Stewart. Dynamic theory for smectic A liquid crystals. *Continuum Mechanics and Thermodynamics*, 18:343–360, 2007.
- [22]. A.A. Doinikov and A. Bouakaz. Theoretical investigation of shear stress generated by a contrast microbubble on the cell membrane as a mechanism for sonoporation. *Journal Acoustical Society of America*, 128:11–19, 2010.